unpatentable over Mullis, et al., in view of Adams, et al., and Hillier, et al.

These rejections are believed to be overcome in part by the amendments and are otherwise traversed for reasons discussed below.

Overview of the Amendments

Claims 14 and 30 have been canceled without prejudice or disclaimer. Claims 1-8, 10, 11, 15, 33, 38, and 39 have been amended without prejudice or disclaimer. Cancellation or amendment of these claims is not intended to be an acquiescence in the Office's assessment of those claims in the 8 July 1999 Communication, and applicants expressly reserve the right to bring the subject matter of the original claims again in a subsequent, related application.

Basis for the amendments to claims 1 and 10 ("reagent polynucleotide") can be found throughout the specification, for example, at the following location: page 22, lines 27-35.

Basis for the amendments to claims 1, 3, 6, and 10 ("indicative of breast disease") can be found throughout the specification, for example, at the following locations: pages 4-5; page 19, lines 30-32; and page 22, lines 27-35.

Basis for the amendments to claims 1, 3, 6, 10, 11, and 33 ("specifically binds") can be found throughout the specification and is extensively discussed in section 1, below.

Basis for the amendments to claims 3, 4, 7, and 10 ("target polynucleotide") can be found throughout the specification, for example, at the following locations: originally presented claim 1; and pages 5 and 6.

Basis for the amendments to claims 1, 3, 6, 10, 11, and 33 ("10 nucleotides") can be found throughout the specification, for example, at the following location: page 13, lines 18-23.

Basis for the amendment to claim 15 ("8 contiguous amino acids") can be found throughout the specification, for example, at the following locations: page 13, lines 18-

23; page 16, lines 3-6; and page 13, lines 3-35. SEQ ID NO:16 was originally referred to, in the examined claims, in claim 38.

Basis for the amendments to claims 38 and 39 ("isolated") can be found throughout the specification, for example, at the following location: page 15, lines 21-28.

Basis for new claims 40-45 (lengths of polynucleotides) can be found throughout the specification, for example, at the following location: page 13, lines 18-23.

Basis for new claims 46-48 (lengths of polypeptides) can be found throughout the specification, for example, at the following locations: page 16, lines 3-6; and page 13, lines 3-35.

Accordingly, no new matter has been added by way of this amendment and the entry thereof is respectfully requested.

Addressing the Examiner's Rejections

1. "Specifically Binds"

In the pending claims the applicants have removed the language "selectively hybridizing" (e.g., original claim 11) and introduced the language "specifically binds." The specification provides extensive basis for use of this language. For example, on page 19, lines 18-29, detection of an analyte is discussed wherein a specific binding member is prepared for binding to a target analyte such as a nucleotide target. On page 20, lines 9-21, a definition of "specific binding members" is discussed, wherein a "specific binding member" is a member of a specific binding pair (see also, e.g., page 20, line 32, to page 22, line 11; and page 5, line 1, to page 6, line 31). That is, two different molecules where one of the molecules, through chemical or physical means, specifically binds to the second molecule. Specific binding pairs can include complementary nucleotide sequences. On pages 22-23, the specification describes how the sequences provided in the application may be used to produce polynucleotide sequences (for example, primers and probes; also see, e.g., page 13, lines 24-31; page 26, lines 5-15) which can be used in assays for the detection of target nucleic acids in test samples, via

specifically binding the polynucleotide sequences to the target. Probes may, for example, be designed from conserved nucleotide regions of the polynucleotides of interest or from non-conserved nucleotide regions of the polynucleotide of interest. The design of such probes for optimization in assays is within the skill of the routineer. Generally, nucleic acid probes are developed from non-conserved or unique regions when maximum specificity is desired, and nucleic acid probes are developed from conserved regions when assaying for nucleotide regions that are closely related to, for example, different members of a multi-gene family or in related species like mouse and man. Numerous examples are given in the specification that would allow one of ordinary skill in the art to determine the metes and bounds of the invention (e.g., Examples 1-9, pages 54-67). For example, selection of primers for use in polymerase chain reactions is described at least on page 26, line 16 to page 27, line 25, and exemplary conditions (including hybridization conditions) for such reactions are described in the Examples (e.g., Examples 3, 8 and 9).

Use of probes in fluorescent in situ hybridization (FISH) technology to perform chromosomal analysis is also described herein. Such an approach can be used to identify cancer-specific structural alterations in the chromosomes, such as deletions or translocations that are visible from chromosome spreads or detectable using PCR-generated and/or allele specific oligonucleotides probes, allele specific amplification or by direct sequencing. Probes also can be labeled with radioisotopes, directly- or indirectly- detectable haptens, or fluorescent molecules, and utilized for *in situ* hybridization studies to evaluate the mRNA expression of the gene comprising the polynucleotide in tissue specimens or cells (page 25, line 27, to page 26, line 2; and Example 7, pages 63-64). Use of the polynucleotide sequences of the present invention in such technology is another example of specific binding of a polynucleotide sequence to a target.

The characteristics and properties of polynucleotides of the present invention for use in hybridization reactions (including probes and amplification primers) are extensively discussed in the specification in the context of specific binding (see, for

example, pages 26-33). Further, examples using polynucleotides in hybridization reactions are discussed in the application, including suitable reaction conditions (e.g., Examples 5, 6, and 7, pages 61-64).

Accordingly, no new matter as been entered by way of this amendment.

2. Rejection of Claims 14 and 30 under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 14 and 30 under 35 U.S.C. §112, first paragraph, asserting that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner asserts that the specification does not enable the skilled artisan to make and use a polynucleotide sequence encoding an epitope of BS106. Applicants disagree with the Examiner's assertion. The specification provides extensive information about the polynucleotide sequence encoding a BS106 polypeptide sequence (e.g., SEQ ID NOs 4 and 16, respectively; see also Example 1, page 55, lines 14-35). The specification provides extensive guidance concerning the identification and use of epitopes of the BS106 polypeptide of the present invention (see, for example -- Example 10, synthetic peptide production; Examples 14-18, expression of coding sequences and analysis of immunogenicity; and page 46-54). However, in order to facilitate prosecution, applicants have canceled claims 14 and 30; applicants expressly reserve the right to bring the subject matter of the original claims 14 and 30 again in a subsequent, related application.

3. Rejection of Claims 1-16, 30, 33, 35, 38 and 39 under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 1-16, 30, 33, 35, 38 and 39 under 35 U.S.C. §112, second paragraph, asserting that the claims are indefinite for failing to particularly

point out and distinctly claim the subject matter which the applicant regards as the invention. The Examiner has asserted the following specific deficiencies in the claims.

A. "Target BS106 polynucleotide"

The Examiner asserts that recitation of "Target BS106 polynucleotide" in claims 1-16, 30, 33, 35, 38 and 39 is unclear.

In order to facilitate prosecution applicants have removed the term "BS106" from the pending claims.

B. "Percent Identity"

The Examiner asserts that recitation of "% identity" in claims 1-16, 33, 35, 38, and 39 is vague and indefinite. Applicants disagree with the Examiner's assessment of the level of enabling disclosure in the present applicant in regard to "percent identity." The applicants discuss the use of available programs for calculating identity or similarity between sequences in the specification (e.g., page 11, line 24, to page 12, line 9). Applicants submit that use of default parameters in such programs is routine and well within the abilities of one having ordinary skill in the art -- this is the manner in which the Examiner has searched the database for sequences that may correspond to the claimed sequences. Further, at the AIPLA meeting in Crystal City, Fall of 1999, Examiner John Doll stated that the USPTO policy toward claims reciting percent identity has changed and that Examiners will no longer be rejecting percent identity claims under 35 U.S.C. §112, second paragraph.

Absolute specificity and precision are not required in the claims. Claims need only reasonably apprize a person having ordinary skill in the art as to their scope. *Hybritech Inc., v. Monoclonal Antibodies, Inc.,* 231 USPQ 81 (Fed. Cir. 1986).

In view of the above amendments and comments the applicants submit that the claims comply with the requirements of 35 U.S.C. §112, second paragraph, and that the rejection of the claims should be withdrawn.

4. Rejection of Claims 11-16, 33, 38 and 39 Under 35 U.S.C. §102(b)

The Examiner has rejected claim 11-16, 33, 38 and 39 under 35 U.S.C. §102(b) asserting that the claims are anticipated by Adams, et al.(GENBANK accession no AA340069, from Nature 377 (6547 Suppl.) 3-174 (1995)) and by Hillier, et al. (Accession no. R75793, 1995). The rejection is applied to the following independent claims: 11, 15, 33, 38, and 39.

The Examiner has cited the rejection over sequence AA340069 (Adams) as a rejection under 35 U.S.C. §102(b). However, the publication (Adams, et al.) cited by the Examiner provides no sequence information; only a recitation of thousands of identification numbers. The date of entry of the sequence information into GENBANK is indicated in the LOCUS line of the MPSRCH results -- the date of entry into GENBANK of AA340069 was 21 April 1997. The filing date of the present application was 31 October 1997. Accordingly, the rejection should be under 35 U.S.C. §102(a). Further, the present application claims priority to U.S. Application 08/742,067, filed 31 October 1996 (referred to as the '067 application). The consensus sequence taught in the '067 application spans nucleotide positions 14 to 482 of the present SEQ ID NO:4. The Adams sequence spans nucleotide positions 18 to 311 of the present SEQ ID NO:4. Accordingly, the AA340069 (Adams) sequence does not constitute effective prior art against the claimed sequences.

The Examiner asserts that Adams, et al., teach a 229 base pair expressed sequence tag (EST), i.e., a polynucleotide, which is about 90% identical to SEQ ID NOs 1-5 of the present application (Office action, page 5, second full paragraph). Further, the Examiner asserts that Hillier, et al., teach a 403 nucleotide EST containing clone which has 87.9%-95% sequence similarity with SEQ ID NOs 1-5 of the present application.

Applicants disagree with the Examiner's assessment of the prior art. The following table summarizes the MPSRCH data provided by the Examiner.

SEQ ID NO. of the present invention	% Identity to R75793*	% Identity to AA340069*
1	87.9	90.1
2	95.1	94.5
3	no homology to this sequence reported in MPSRCH results	no homology to this sequence reported in MPSRCH results
4	66	60.4
5	57.1	52.3
16	no homology to this sequence reported in MPSRCH results	no homology to this sequence reported in MPSRCH results

*Based on MPSRCH data, "Query Match" value

In particular, applicants note that none of the sequences cited by the Examiner teach the polypeptide sequence presented as SEQ ID NO:16 (recited in originally presented claim 38). As noted above, the AA340069 (Adams) sequence does not constitute effective prior art against the claimed sequences. Accordingly, that leaves only the R75793 (Hillier) sequence to address as prior art. (For sequence alignments based on the MPSRCH results see the accompanying Appendix.)

Further, the prior art sequence (R75793) cited by the Examiner does not teach fragments of the recited prior art sequence only the full length sequence itself. The prior art provides no reason that the particular prior art sequence used by the Examiner, which represents one sequence out of a huge number of polynucleotide and polypeptide sequences (i.e., GENBANK or EMBL), would be specifically selected to generate probe and/or primer fragments. Only the complete sequence is available as prior art for purposes of anticipation.

For prior art to anticipate under 35 U.S.C. 102 it has to meet every element of the

claimed invention: such a determination is one of fact. *Hybritech Inc. v. Monoclonal Antibodies*, 802 F.2d at 1367, 231 USPQ 81 (Fed. Cir. 1986).

The prior art cited by the Examiner fails to teach at least the following limitations of the pending independent claims:

{independent claims 11 and 33) a polynucleotide having at least about 10 nucleotides that (i) specifically bind, and (ii) have at least 90% identity with a polynucleotide selected from the group consisting of SEQUENCE ID NO 1; SEQUENCE ID NO 3; and complements thereof;

{claim 15} a polynucleotide sequence that encodes a polypeptide of at least 8 contiguous amino acids derived from SEQUENCE ID NO:16;

{claim 38}a protein comprising an amino acid sequence with at least 90% identity with SEQUENCE ID NO 16; and

{claim 39} DNA having at least 90% identity with SEQUENCE ID NO 4 or SEQUENCE ID NO 5.

In view of the above amendments and arguments, the cited reference sequences cannot be said to teach all the elements of the present invention. The dependent claims distinguish over the prior art at least in view of their dependencies on the independent claims. Accordingly, there is no support for the pending claims being anticipated by the cited prior art under 35 U.S.C. §102(b) and withdrawal of the rejection is respectfully requested.

5. Rejections of the Claims Under 35 U.S.C. §103

The Examiner has rejected claims 1-10 and 35 under 35 U.S.C. §103(a) as being unpatentable over Mullis, et al., in view of Adams, et al., and Hillier, et al.

The combination selected by the Examiner is only the result of hindsight reconstruction. The Examiner has taken a reference teaching general methods of molecular biology (Mullis) and combined it with two specific sequences (Adam and Hillier), where the prior art contains no guidance concerning the selection of those two

specific sequences from among the millions of possible sequences available in the database (i.e., GENBANK or EMBL) from which the two specific sequences (only one of which is effective prior art) were drawn .

Obviousness cannot be established by combining teachings in the prior art absent some teaching or suggestion in the prior art that the combination be made. E.g., *In re Stence,* 828 F. 2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987); *In re Newell,* 891 F. 2d 899, 13 USPQ2d 1248 (Fed Cir 1989). In particular, the fact that references can be combined does not make the combination obvious unless the prior art also contains something to suggest the desirability of that combination. *In re Sernaker,* 702 F.2d 989, 217 USPQ 1 (Fed,. Cir. 1983).

Further, the currently pending independent claims each recite a limitation similar to the following: "a method of detecting the presence of a target polynucleotide indicative of breast disease." None of the references singly or in combination teach that detection of the polynucleotides of the present invention may be indicative of breast disease (e.g., see Figures 3A, 3B, 4A, and 4B, and related disclosures of the present specification).

The PTO has the burden of establishing a case of *prima facie* obviousness, and can meet this burden "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Fine,* 837 F.2d 1071, 5 USPQd2 1596 (Fed. Cir. 1988). No such objective teaching has been presented.

Accordingly, because the elements of the claimed invention are not taught by the cited references, the applicants submit that the rejections under 35 U.S.C. §103 should be withdrawn.

CONCLUSION

Applicant respectfully submits that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice

of Allowance is believed in order and is respectfully requested.

If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

Please direct all further communications in this application to:

Cheryl L. Becker, Esq.
Abbott Laboratories
D-377/AP6D-2
100 Abbott Park Road
Abbott Park, IL 60064-3500
Telephone: (847) 935-1729
Facsimile: (847) 938-2623.

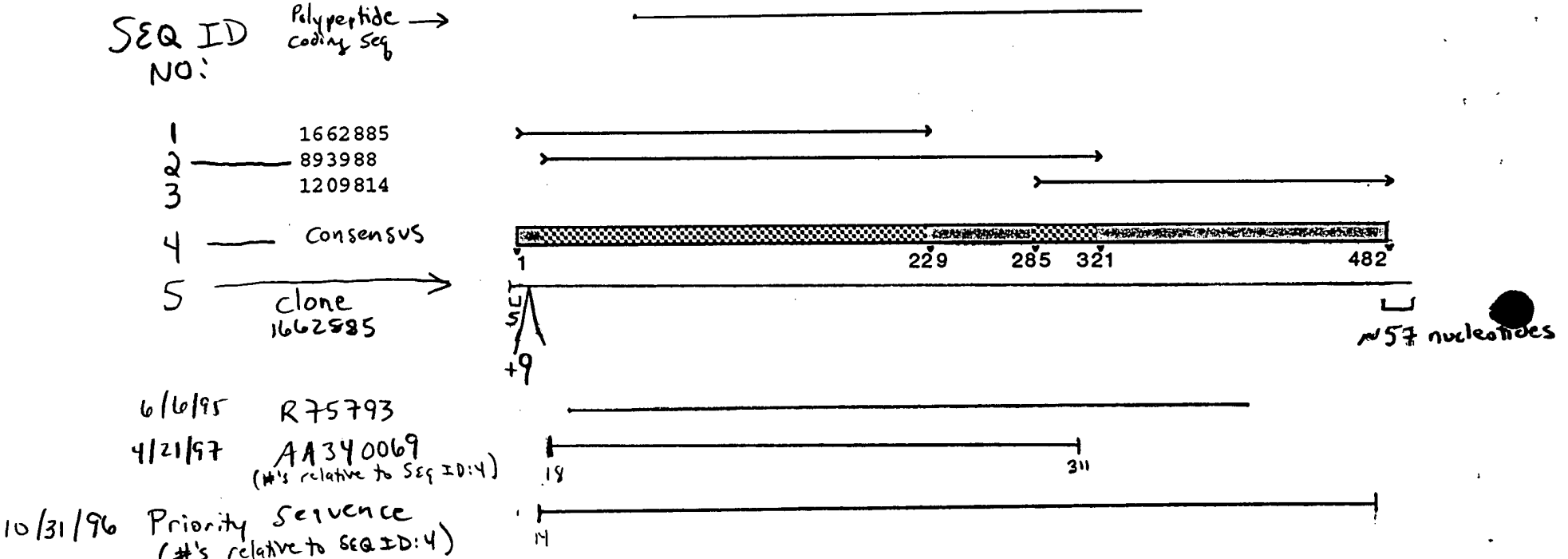
Respectfully submitted,

Date: 8 Dec 1999

By: Gary R Fabian

Gary R. Fabian, Ph.D.
Registration No. 33,875
Agent for Applicants

ABBOTT LABORATORIES
D-377/AP6D-2, 100 Abbott Park Road
Abbott Park, IL 60064-3500
Telephone: (847) 935-1729
Facsimile: (847) 938-2623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4/21/97 AA340069
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APPENDIX